## REMARKS

Claims 20, 49, 51, 57, 59 and 65-69 previously were pending in the subject application. Applicants hereby resubmit the claims as previously pending together with the arguments set forth below. Applicants respectfully request that the Examiner enter this Response and consider the following remarks.

### I. Rejections and Responses

In the previous office action (dated April 29, 2009), the Examiner rejected the claims as then pending on enablement, obviousness, and non-statutory obviousness-type double-patenting grounds. Applicants contested the enablement and obviousness rejections on the merits and further amended the claims, and argued that a terminal disclaimer was not then appropriate since the double-patenting rejection was provisional. In the pending office action, the Examiner has withdrawn the enablement rejections in view of the amended claims. As detailed below, the Examiner also appears to have been persuaded by Applicants' response to the obviousness rejection, and has set forth a different basis for rejecting the claims as obvious over the same asserted references. The Examiner has maintained the obviousness-type double-patenting rejection. Applicants argue that the pending rejections should be withdrawn for the reasons set forth below.

#### A. 35 U.S.C. § 103

**Rejection**

The Examiner has rejected claims 20, 49, 51, 57, 59, and 65-68 as allegedly obvious over U.S. Patent No.7,494,644 ("Lee") and Qu et al. (Circ. Res. 89: e9 (2001), of record). Applicants understand that the rejection is intended to apply as well to dependent claim 69, which was added in the previous amendment. According to the Examiner, Lee teaches compositions that comprise mammalian cells such as mesenchymal stem cells ("MSCs") "genetically engineered to express connexin 43 (Cx43) protein intended for establishing electrical coupling between cardiomyocytes" and the recombinant cells. Office Action at 3. According to the Examiner, Lee also teaches a "method of establishing electrical coupling between cardiomyocytes and

recombinant mammalian cells" engineered to express Cx43 protein. *See id.* at 3. The Examiner recognizes that "electrical coupling" "allows for intracellular communication" so as to provide for "electrical conduction between the cells." *See id.* The Examiner further states that Lee discloses a method that uses such recombinant cells to "establish an electrical connection between the recombinant cell" and a host myocardial cell in order to treat "a cardiac conduction disturbance in a host." *See id.* at 3-4. The Examiner concedes that Lee does "not disclos[e] MSC comprising nucleic acid encoding HCN2." *Id.* at 4.

According to the Examiner, Qu et al. discloses that treatment of adult and neonatal cells in culture with an "adenoviral construct comprising nucleic acid encoding HCN2" "resulted in expression of high current levels, with faster activation in neonate." *See* Office Action at 4.

The Examiner considers Qu et al. to compensate for the acknowledged deficiency of Lee. The pending rejection relies on a rationale different than that of the previous rejection. The previous rejection was based on an alleged motivation to modify Lee by replacing a nucleic acid encoding Cx43, used by Lee, "with another gene such as HCN2." *See* Office Action (April 29, 2009) at 8. The Examiner appears to have been persuaded by Applicants' argument in the previous amendment that the person of ordinary skill in the art would not have been motivated to make such a substitution. The pending rejection thus is based on an alleged motivation to modify Lee, not by replacing Cx43 with HCN2, but by including a nucleic acid encoding HCN2 in addition to the nucleic acid encoding Cx43. According to the Examiner,

> [i]It would have been obvious for one of ordinary skill in the art at the time of invention to modify the composition disclosed by Lee by including the gene of interest HCN2 as disclosed by Qu. One of ordinary skill in the art would be motivated to do [sic] use HCN2 as Qu had already shown that HCN2 could be expressed in mammalian cells to induce pacemaker current.

Pending Office Action at 4. *See also id.* at 5 (stating that Applicants' claimed composition comprises any MSCs incorporated with a nucleic acid that encodes HCN2, including MSCs that are further genetically modified with, e.g., a nucleic acid encoding Cx43).

The Examiner further states that the person of ordinary skill in the art would reasonably have expected such MSCs to form gap junctions when administered to the heart because "Lee

taught hMSCs engrafts in the myocardium and forms gap junction with recipient MCS." *Id.* at 4.

**Response**

Applicants believe that the pending claims should be allowed because the claims should not be considered obvious on the grounds set forth by the Examiner. As detailed below, there is no teaching or suggestion in the prior art to include an additional nucleic acid encoding HCN2 in the hMSCs of Lee. Further, Lee in fact teaches away from including an additional nucleic acid.

**No motivation to modify Lee**

Claims 20, 49, 51, 57, 59, and 65-69 would not have been *prima facie* obvious on the grounds set forth by the Examiner because the person of ordinary skill in the art would not have been motivated to modify Lee's disclosure as the Examiner proposes. As the Examiner recognizes, Lee teaches "methods for establishing electrical coupling between cardiomyocytes and recombinant cells which have been genetically engineered to express a connexin protein such as connexin 43 (Cx43) protein." Lee at col. 3, ll. 25-28. Further, Lee's purported "invention is based on the discovery that genetic modification of skeletal muscle cells to express a recombinant connexin, enables the genetically modified cells to establish electrocommunication with cardiac cells via gap junctions." *Id.* at col. 3, ll. 28-32 (emphasis added). Further, according to Lee, "[p]roduction of connexin in the recombinant cell provides for an electrical conection." Lee at col. 11, ll. 1-2. Lee focuses on the use of skeletal muscle cells for contractility; Lee teaches that such cells should be transformed with connexins to establish electrical connections with cardiac cells.

Further, the secondary Qu et al. reference does not cure the deficiencies of Lee, acknowledged by the Examiner to be Lee's failure to teach or suggest the incorporation of an HCN-encoding nucleic acid into the cells introduced into the heart. Qu et al. simply attempts to provide an explanation for the observed phenomenon that "[v]entricular pacemaker current ($I_f$) shows distinct voltage dependence as a function of age, activating outside the physiological range in normal adult ventricle, but less negatively in neonatal ventricle" even though "heterologously expressed HCN2 and HCN4, the putative molecular correlates of ventricular $I_f$,

exhibit only a modest difference in activation voltage." Qu et al. at e8. The authors conclude that "the developmental difference in pacemaker current voltage dependence under our experimental conditions is largely accounted for by an effect of the myocyte maturational state on the HCN2 isoform." *Id.* at e12.

Qu et al. thus does not discuss mesenchymal stem cells or their use to deliver genes to the heart or to treat a cardiac rhythm disorder or induce a current in a heart. Specifically, Qu et al. does not teach or suggest that a nucleic acid encoding an HCN can be delivered to a heart via a mesenchymal stem cell. Rather, the only expression experiments discussed by Qu et al. entail infection of rat ventricular myocytes with an adenoviral construct comprising an HCN2-encoding DNA fragment. The deficiency of Lee, recognized by the Examiner, thus is not cured by Qu et al.; Qu et al. would not have motivated the person of ordinary skill in the art to modify Lee to arrive at the claimed compositions or methods.

**Lee teaches away from the modification asserted by the Examiner**

According to the current office action, Lee teaches that the cells used according to Lee's disclosure can be transfected with an additional nucleic acid, citing Lee at column 13, line 10. Office Action at 6. The cited passage, however, undermines the Examiner's argument and supports the Applicants' position. The cited passage reads as follows:

> The recombinant cells can optionally be genetically modified to express other proteins, such as N-cadherin protein. However, the cells are preferably are [sic] not so modified so as to avoid additional genetic manipulation of the cell to be transplanted. Furthermore, the recombinant cell need not be modified to express or overexpress N-cadherin, as the inventors here have shown that expression of an exogenous (e.g., introduced or recombinant) connexin (either in the presence or absence of expression of any endogenous connexin) is sufficient.

Lee at col. 13, ll. 10-19.

This passage reveals two flaws in the Examiner's argument. First, to the extent that Lee teaches that the cells can be genetically modified, Lee provides no suggestion that the other genes should encode a protein relevant to pacemaking. To the contrary, Lee suggests a gene that encodes N-cadherin, which, like connexin 43 that Lee introduces into cells, is involved in cell-

cell connection. *See, e.g.*, Lee at col. 11, ll. 5-20 and Bruce Alberts *et al.*, Molecular Biology of the Cell 966 (3d ed. 1994) ("Alberts") ("The cadherins are responsible for $Ca^{2+}$-dependent cell-cell adhesion in vertebrate tissues."). There is thus no teaching or suggestion to modify Lee's disclosure by introducing a nucleic acid wholly unrelated to the aim of Lee. Lee aims to "effect cardiac repair" by transplanting (into the heart) cells that electrically couple to endogenous cardiomyocytes. *See* Lee at col. 3, ll. 17-21. Lee therefore only suggests using nucleic acids related to achieving electrical coupling. *See* Lee at col. 3, ll. 6-10 (stating that "N-cadherin and connexin 43 were both detected at the contact sites between cardiomyocytes and skeletal myotubes" in an in vitro study). Such a limited suggestion would not encompass the use of other nucleic acids, such as a nucleic acid that encodes HCN2. The person of ordinary skill in the art therefore would not have been motivated to combine Lee with a reference such as Qu that is concerned with nucleic acids that encode proteins unrelated to electrical coupling of cells.

Second, the very passage the Examiner cites actually teaches that further genetic modification is optional but that "the cells are preferably are not so modified." Lee thus actively discourages genetic manipulation of the cells other than to incorporate a connexin. Lee therefore teaches away from incorporating the cells with an additional nucleic acid, such as a nucleic acid that encodes HCN2. That it is preferred "to avoid additional genetic manipulation of the cell" (Lee at col. 13, ll. 12-14) suggests that such manipulation might interfere with the desired results. Lee's teaching is therefore contrary to the Examiner's contention that Lee suggests incorporating into the stem cells a nucleic acid in addition to the Cx43-encoding nucleic acid, and that that nucleic acid could encode HCN2. *See, e.g.*, *In re Hedges*, 783 F.2d 1038, 1041 (Fed. Cir. 1986) (finding that the prior art leads away from the claimed invention, reasoning that "'[i]t is impermissible within the framework of section 103 to pick and choose from any one reference only so much of it as will support a given position, to the exclusion of other parts necessary to the full appreciation of what such reference fairly suggests to one of ordinary skill in the art'" (quoting *In re Wesslau*, 353 F.2d 238, 241)) and *In re Baird*, 16 F.3d 380, 382-83 (Fed. Cir. 1994) (stating that the Knapp reference "appears to teach away from the selection of bisphenol A by focusing on more complex diphenols . . . . Fifteen typical diphenols are recited. None of them, or any of the other preferred phenols recited above, is or suggests bisphenol A.").

Further, Qu would not have provided a motivation to add a nucleic acid encoding HCN2 to Lee's connexin-expressing cells because, as noted above, Qu was strictly concerned with explaining a natural phenomenon and not with any potential clinical uses of HCN2. The mere discussion of HCN2 or its pacemaking properties should not be considered motivation to use it in Lee's cells, which are intended merely to achieve electrical connectivity with the cells of the heart into which they are transplanted, particularly when Lee leads away from any such modification.

### B. Non-statutory Double Patenting

#### Rejection

The Examiner has provisionally rejected claims 20, 49, 51, 57, 59, and 65-67 under the judicially created doctrine of obviousness-type double patenting as allegedly unpatentable over claims 12, 39, 65, 67-68, and 73-76 of co-pending Application No. 10/342,506 ("the '506 application"), which corresponds to U.S. Publication No. 20040137621, "in view of U.S. Patent No. 6,979,532 ("Jansen et al.")."

#### Response

To expedite prosecution, Applicants submit together with this response a terminal disclaimer over the '506 application, the claims of which have been allowed.

## CONCLUSION

In view of the remarks made hereinabove, Applicants respectfully request that the Examiner reconsider and withdraw the rejections set forth in the January 21, 2010 Final Office Action, and earnestly solicit allowance of the now pending claims.

If a telephone interview would assist in expediting prosecution of the subject application, the Examiner is invited to telephone the undersigned at the number provided below. No fee is deemed necessary in connection with the filing of this Amendment. However, if any fee is required, authorization is hereby given to charge the amount of any such fee to Deposit Account No. 11-0600.

Respectfully submitted,

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